Claim 20 (amended) A composition for treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effect of free radicals on cellular membranes and other organelles during a period of increased capillary permeability which comprises at least one polysaccharide selected from the group consisting of hydroxyethyl starch and dextran and at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C, in admixture with a pharmaceutically acceptable liquid carrier.

Remarks

Claims 1 to 20 are in the application. Claims 1 and 20 have been amended. As amended, all of the method claims and the composition claim are directed to a method of treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions during a period of increased capillary permeability and for preventing the harmful effects of free radicals on cellular membranes and other organelles. The method comprises (claim 1) administering to a subject an effective amount of composition comprising at least one polysaccharide selected from hydroxyethyl starch and dextran of varying molecular sizes and at least one of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C.

The Examiner has rejected all of the claims in the application as obvious over Zikria in view of Weiss, Munkes and Gerdin.

It is the Examiner's position that Zikria teaches the use of hydroxyethyl starch and

hydroxyethyl dextran as a means for treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions. The Examiner concedes that Zikria does not teach the use of antioxidants along with the hydroxyethyl starch or hydroxyethyl dextran. (It is noted that the application and claims recite "hydroxyethyl starch and dextran" and not hydroxyethyl starch and hydroxyethyl dextran).

Weiss (superoxide dismutase), Munkres (cAMP) (hydroxyethyl rutoside) are relied as supplying this omission. Specifically the Examiner states that it would have been obvious to modify Zikria "by adding any art recognized antioxidant molecule such as Vitamin C, superoxide dismutase, catalase glutathione peroxidase, hydroxyethyl rutoside or cAMP (as suggested by Weiss, Munkres and Gerdin) for the expressed purpose of protecting capillary endothelial junctions from oxidate damage that would lead to the leakage of serum proteins."

As noted above and in the specification, the leakage from the capillary endothelial junctions during a period of increased permeability is accomplished by the administration of the hydroxyethyl starch and/or dextran. The antioxidant portion of the composition serves to prevent pathology due to the activity of free radicals.

Zikria teaches a method for preventing leakage of serum albumin from capillary endothelial junctions during a period of increased capillary permeability. That and the method for doing this, i.e., administering certain macromolecules. For example HES, intravenously is all that the Zikria Patent teaches. It does not suggest including an antioxidant for preventing pathology, damage to cells, tissues or organs due to free radical activity.

The Weiss reference provided by the Examiner is almost entirely unreadable. If the

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Examiner continues his rejection based on this reference, a readable copy should be provided the applicant. The Weiss work is directed to determining the effect the effect of superoxide in the destruction of erythrocyte targets by human neutrophils. The destruction mechanism involves O_2 mediated methemoglobin formation with the resultant formation of a cytotoxic peroxide ferrihomo complex. The key to the study was the utilization of the human neutrophil as the source of the oxygen metabolite as this permitted insight into the physiological mechanisms of the target cell destruction and host defense. Superoxide dismutase is one of the materials used. As reported at page 9913 the superoxide dismutase (copper-zinc superoxide dismutase) in an experiment to determine the role of O_2 in hemolysis inhibited cytotoxicity. This isolated and very special experimental result is not seen to suggest to the skilled in the art the use of antioxidant in conjunction with a macromolecule solution as taught by the applicant.

The only suggestion comes from the applicant's specification which is clearly not available. The teaching or suggestion to modify must come from the reference and there is no such teaching here.

Munkres is also a report on the very specific finding and namely that mutants of Neurospora are deficient in certain antioxidants including superoxide dismutase and cAMP and that their survival can be enhanced by "dietary" cAMP or superoxide dismutase. Absolutely nothing in this abstracted experiment suggests combining the macromolecule disclosed by Zikria with the antioxidant disclosed for increasing the survival of mutant Neurospora and that such combination could be administered intravenously for preventing leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effects of free

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radicals on cellular membranes and organelles.

This teaching is found only in the applicant's disclosure and cannot be relied on by the Examiner.

Gerdin in the reported abstract discloses that the flavonoid o-(β-hydroxyethyl) rutoside has an inhibitory effect on increased micro vascular permeability induced by various agents in rat skin.

The applicant does not propose that rutoside is effective to inhibit micro vascular permeability (the macromolecule HES or dextran does this) but rather that hydroxyethyl rutoside is effective as an antioxidant to combat pathology due to activity of free radicals.

This reference has been selected as have the previously discussed references by the Examiner by the picking and choosing of references with a view to arriving at, by modification of the primary reference, the claimed invention.

Not one of these secondary references suggests in any way the modification of a treatment solution as taught by Zikria to include an antioxidant so that the administration intravenously to a subject in dire straits of the solution prevents leakage of macromolecules, for example, albumin, from the capillary endothelial junctions and at the same time prevents damage to the cellular membranes and other organelles due to the presence of released free radicals.

In the absence of such a suggestion in the references themselves, the picking and choosing of references having different objectives and different treatment mechanisms of isolated antioxidants does not negative the applicant's invention.

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Reconsideration and allowance of the claims in the application are respectfully requested.

It is respectfully requested that an extension of time of one (1) month be granted so that the response will be timely if received in the Office by September 11, 1998.

The required fee is enclosed.

Respectfully submitted,

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Certificate of Mailing
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231, on the 8th Day of Sept, 1998.

E M. Sommer

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